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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOLT, ANDRIAE M	

ART UNIT	PAPER NUMBER
1616	

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12/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,082	HIGGINS ET AL.	
	Examiner	Art Unit	
	Andriae M. Holt	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *2-5,7,10,13-17,24-32 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,9,11,12,18-23 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/15/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The new examiner of record is Andriae M. Holt.

Claims 1-34 are pending in the application

Election/Restrictions

Applicant's election without traverse of chronic obstructive pulmonary disease (COPD) as the specifically named pathological change and compound 93 as the compound capable of inhibiting TGF-signaling in the reply filed on May 4, 2007 is acknowledged.

Claims 2-5, 7, 10, 13-17, 24-32 and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 4, 2007.

Claims 1-34 are pending in this application. Claims 2-5, 7, 10, 13-17, 24-32 and 34 have been cancelled. Claims 1, 6, 8-12, 18-23 and 33 will be examined on the merits.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) is acknowledged. Benefit of US Provisional Application 60/428,860 filed November 22, 2002 is acknowledged.

Information Disclosure Statement

Receipt of Information Disclosure Statements filed on August 15, 2005 is acknowledged.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

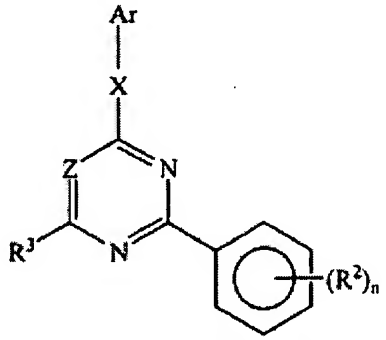
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 22-23 are provisionally rejected on the ground of nonstatutory double patenting over claims 40-43 of copending Application No. 10/440,428. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant

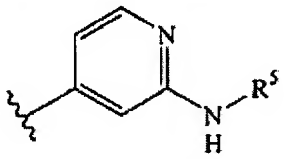
application are claiming common subject matter, as follows: Each application is to a method of treating a fibroproliferative disease associated with enhanced TGF-β activity in a subject, by administering to the subject an amount of dexamethasone (corticosteroid, instant application) and a TGF-β inhibitor which specifically binds to at TGFβ-R1 receptor, that is effective to inhibit the enhanced TGF- β activity, wherein the TGF- β inhibitor is a compound of the following formula:



(4)

and the pharmaceutically acceptable salts and prodrug forms thereof; wherein

Ar represents an optionally substituted aromatic or optionally substituted heteroaromatic moiety containing 5-12 ring members wherein said heteroaromatic moiety contains one or more O, S, and/or N with a proviso that the optionally substituted Ar is not



wherein R^5 is H, alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), an aromatic or heteroaromatic moiety containing 5-11 ring members;

X is NR^1, O, or S;

R^1 is H, alkyl (1-8C), alkenyl (2-8C), or alkynyl (2-8C);

Z represents N or CR^4;

each of R^3 and R^4 is independently H, or a non-interfering substituent;

each R^2 is independently a non-interfering substituent; and

n is 0, 1, 2, 3, 4, or 5.

[0020] In one embodiment, if n>2, and the R2's are adjacent, they can be joined together to form a 5 to 7 membered non-aromatic, heteroaromatic, or aromatic ring containing 1 to 3 heteroatoms where each heteroatom can independently be O, N, or S.

Claims 41-42 define the fibroproliferative disease as pulmonary, including chronic obstructive pulmonary disease (COPD). Claim 43 defines the subject as being human, a mammalian subject in the instant application.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claims 1, 18-19, 22-23 and 33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 10 and 19 of copending Application No. 10/626,004. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of instant application is to a method of treating chronic obstructive pulmonary disease (COPD) by administering to a mammalian subject in need an effective amount of a compound capable of inhibiting TGF-β signaling through a TGF-β receptor and a corticosteroid. Claims 22-23 and 33 define the compound as a non-peptide small molecule of formula (4), referenced above. Claim 1 of the co-pending application is a method for the improvement of lung function by administering to a mammalian subject diagnosed with a disease or condition benefiting from the improvement of lung function an effective amount of a molecule capable of inhibiting a biological activity mediated by a TGFβ-R1 kinase receptor. Claim 2 of the co-pending application defines the conditions including COPD. The small organic molecule of the co-pending application is the same compound of formula 4, referenced above. The compound is formula 2 of the co-pending application. It would have been obvious to one of ordinary skill in the art at the time of invention that if you treat chronic obstructive pulmonary disease with a compound of formula 4 (instant application), which is the same as formula 2 of the co-

pending application, that is capable of inhibiting TGFβ-R1 kinase that one would reasonably expect to get an improvement in lung function as claimed in the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 33 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "salts", does not reasonably provide enablement for "prodrugs". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention in the instant case has claims which embrace pyrimidine compounds that are capable of inhibiting TGF-β signaling. The scope of "prodrug" is not adequately enabled. Applicants provide no guidance as how the compounds are made more active *in vivo*. The choice of a "prodrug" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrugs will be suitable for the instant invention.

The instant compounds of formula (4) wherein the prodrugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by said claims. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Chakravarty et al. (US 6,277,989).

Chakravarty et al. teach methods and compounds useful in treating conditions that are characterized by enhanced TFG-β activity. Chakravarty et al. teach the conditions include inflammation, proliferative diseases and certain cardiovascular disorders (col. 2, lines 60-65). Chakravarty et al. further teach conditions "characterized by enhanced TGF-β activity" include those wherein TGF-β synthesis is stimulated so that TGF-β is present in enhanced amount or wherein TGF-β latent protein is undesirably activated or converted to active TGF-β protein or wherein TGF-β receptors are upregulated or wherein the TGF-β protein shows enhanced binding to cells or extracellular matrix in the

location of the disease. Chakravarty et al. teach that in either case, "enhanced activity" refers to any condition wherein the effectiveness of either of these proteins is undesirably high, regardless of the cause (col. 3, lines 41-51). Chakravarty et al. further teach these conditions include progressive pulmonary and bronchial fibrosis (col. 3, lines 61-63). Chakravarty et al. teach that the compounds useful in the invention are derivatives of quinazoline and related compounds containing mandatory substituents at positions corresponding to the 2- and 4-positions of quinazoline (col. 4, lines 7-10). Chakravarty et al. teach the compounds provide beneficial effect in treating diseases such as chronic obstructive pulmonary disease (COPD) (col. 15, line 30-40). Chakravarty et al. teach that the inhibitors of TGF-β or dual inhibitors of p38 kinase and TGF-β, can be used as single therapeutic agents or in combination with other therapeutic agents (col. 19, lines 40-45). Chakravarty et al. further teach that drugs that can be usefully combined with other therapeutic compounds include natural or synthetic corticosteroids (col. 19, lines 44-45). Chakravarty et al. teach that as the compounds of the invention are small molecules, they are conveniently administered by oral administration by compounding them with suitable pharmaceutical excipients so as to provide tablets, capsules, syrups and the like (col. 18, lines 62-66) (claims 22-23, non-peptide small molecule, instant invention).

Chakravarty et al. teach that TGF-β is active as a homodimer, but is synthesized and secreted from cells as an inactive latent complex of the mature homodimer and proregions, called latency associated protein (LAP) (col. 18, lines 4-7). Chakravarty et al. teach that other than v6 there is a variety of cell surface proteins/receptors that

transducer the signals initiated by binding of the active TGF-β ligand to its receptors. Chakravarty et al. further teach these include types I, II, III, IV and V (col. 18, lines 20-24). Chakravarty et al. teach type IV is present only in the pituitary gland while the others are ubiquitous (col. 18, lines 20-24).

It is inherent that if a compound is capable of inhibiting TGF-β signaling through a TGF-β receptor and a corticosteroid, that the compound is capable of inducing change in the activity or signaling of a steroid hormone receptor and that the compound is capable of binding to an additional receptor kinase such as activin receptor (Alk 4), as it is known in the art that activin receptors modulate signals for ligands belonging to TGF-β.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6, 8-9, 11-12, and 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakravarty et al. (US 6,277,989) in view of Sporn et al. (Pharmacology,1990).

Applicant's Invention

Applicant claims a method for treating chronic obstructive pulmonary disease (COPD) by administering to a mammalian subject an effective amount of a compound of inhibiting TGF-β signaling through a TGF-β receptor and a corticosteroid. Applicant claims the compound capable of inhibiting TGF-β is a non-peptide small molecule.

Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Chakravarty et al. are referenced herein above and will be used in the instant rejection.

Difference between the prior art and the claims

(MPEP 2141.02)

Chakravarty et al. do not teach the specific receptors. It is for this reason Sporn et al. is joined.

Sporn et al. teach that TGF-β is mediated through binding of specific cell membrane receptors (page 429-431, section D). Sporn et al. teach that TGF-β has the potential to mediate the actions of retinoids and steroids. Sporn et al. teach that the actions on cells of low molecular weight molecules such as retinoids and of hormones

such as estrogen and dexamethasone might be mediated at least in part, by TGF-β (page 451-452, Section III). Sporn et al. further teach that in several examples, the biological effects of TGF-β and the hormone modifier are similar (page 452, Section III). Sporn et al. teach both tamoxifen and TGF-β inhibit the growth of breast cancer cell lines, both estrogen and TGF –β induce collagen synthesis in bone cells and both retinoic acid and TGF-β inhibit proliferation of various epithelial. Sporn et al. further teach that with the recent discovery and cloning of the superfamily of regulatory proteins that includes receptors for the steroid hormones including vitamin D3, for thyroid hormone and for retinoic acid, it should be possible to test directly at the molecular level whether these trans-acting enhancer factors might lead to relationships between the actions of hormones, vitamins and growth factors on cells.

Finding of prima facie obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the two cited references to formulate a method for treating chronic obstructive pulmonary disease (COPD) because Chakravarty et al. teach it is within the skill of the art to use a compound capable of inhibiting TGF-β over activity by administering an amount of the compound to a subject with COPD. Chakravarty et al. also teach it is within the skill of the art to combine those compounds with other drugs, such as corticosteroids. Sporn et al. teach that TGF- β has the ability to mediate the actions of steroids. One would have been motivated to make this combination in order to receive the expected benefit of administering a compound or

medicament that inhibits TGF- β signaling in combination with a corticosteroid to a patient suffering from COPD that would provide the patient with a medication combination that is improve their symptoms and that would enhance the benefits of the co-drug. Given the state of the art as evidenced by the teachings of the cited references, and absent any evidence to the contrary, there would have been a reasonable expectation of success in combining the teachings of the cited references to produce a medication that would be effective and safe in relieving the patient of their symptoms.

In reference to claim 33, examiner searched applicant's elected species, compound 93, and was unable to find the compound. Examiner expanded the search using formula 4, set forth in claim 33 of the instant invention.

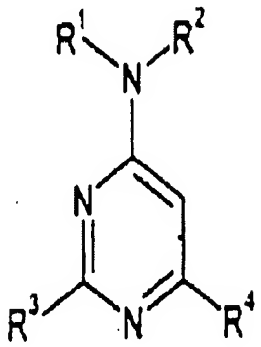
Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schindler et al. (CA 2,340,405) in view of Arnold et al. (WO 200017202).

Applicant's Invention

Applicant claims a method of use of a small organic molecule of formula (4) referenced above, to treat chronic obstructive pulmonary disease.

Determination of the scope of the content of the prior art (MPEP 2141.01)

Schindler et al. teach compounds of formula (I)



I

in which R1, R2, R3 and R4 have the meanings given in the specification on page 4, lines 5-30 -page 6, lines 1-29 (claim 33, formula 4, instant invention). Schindler et al. teach that the compounds of formula I bring about an increase in the cGMP concentration by means of the activation of soluble guanylate cyclase and are therefore valuable agents for the treatment and prophylaxis of illnesses which are associated with a low or reduced cGMP level (page 16, lines 24-30). Schindler et al. teach illnesses and pathological conditions which are associated with a low cGMP level or in which an increase in the cGMP level is desired include cardiovascular disorders, and bronchial asthma (page 16, lines 33-37-page 17, lines 1-3). Schindler et al. further teach the compounds of formula (I) can be used in humans as pharmaceuticals (page 17, lines 8-10).

Difference between the prior art and the claims

(MPEP 2141.02)

Schindler et al. do not teach the treatment of COPD. It is for this reason Arnold is joined.

Arnold et al. teach 4-aminopyrrolopyrmidines of formula (I) that are used for the inhibition of protein kinase mediated disorders, particularly in treatment of angiogenesis, COPD, and asthma. Arnold et al. further teach the compositions of the present invention may be associated with other compatible pharmacologically active ingredients, for example compounds that reduce inflammation, anti-inflammatory or anti-edemic steroids (corticosteroids, instant invention).

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the pyrimidine compound of formula (I) to treat chronic obstructive pulmonary disease (COPD) in combination with a corticosteroid because Schindler et al. teach it is within the skill of the art to use pyrimidine compounds to treat bronchial asthma and Arnold et al. teach it is within the skill of the art to use pyrimidine compounds to treat asthma and COPD in combination with steroids. One would have been motivated to make this combination in order to receive the expected benefit of administering a compound or medicament that would provide the patient with a medication combination that is improve their symptoms and that would enhance the benefits of the co-drug. Given the state of the art as evidenced by the teachings of the cited reference, and absent any evidence to the contrary, there would have been a reasonable expectation of success in combining the teachings of the cited references to produce a medication that would be effective and safe in relieving the patient of their symptoms.

None of the claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andriae M. Holt whose telephone number is 571-272-9328. The examiner can normally be reached on 7:00 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richter Johann can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free)? If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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